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Methadone Pharmacology

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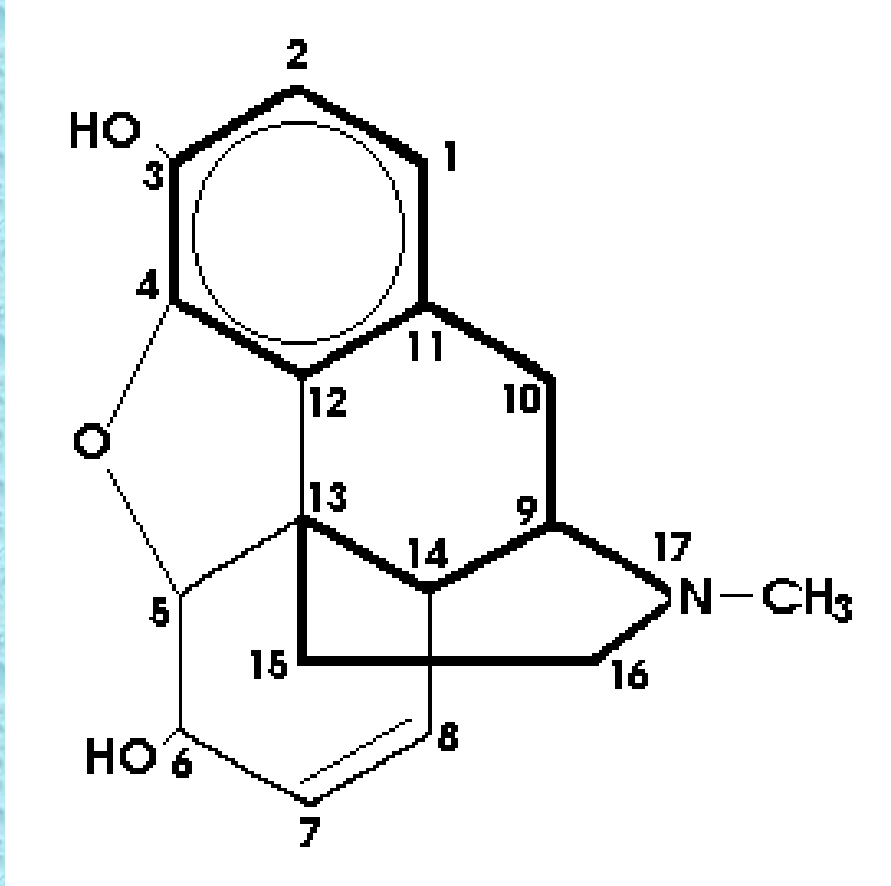
- Methadone was synthesized by German chemists during Wold War II when cut off their opium supply.
- It is difficult to fight a war without analgesics, Germans went to work and synthesized a number of medications in use today, including **demerol** and **darvon** structurally similar to methadone.

- Methadone, or dolophine
- (Hoechst 10820 or polamidon)
- "adolphine" or "adolophine" or "Dolphamine (Adolf Hitler)
- Dolophine actually comes from the German Dolphium. The name derives from the Latin dolor which means "pain" and finis which means "end".

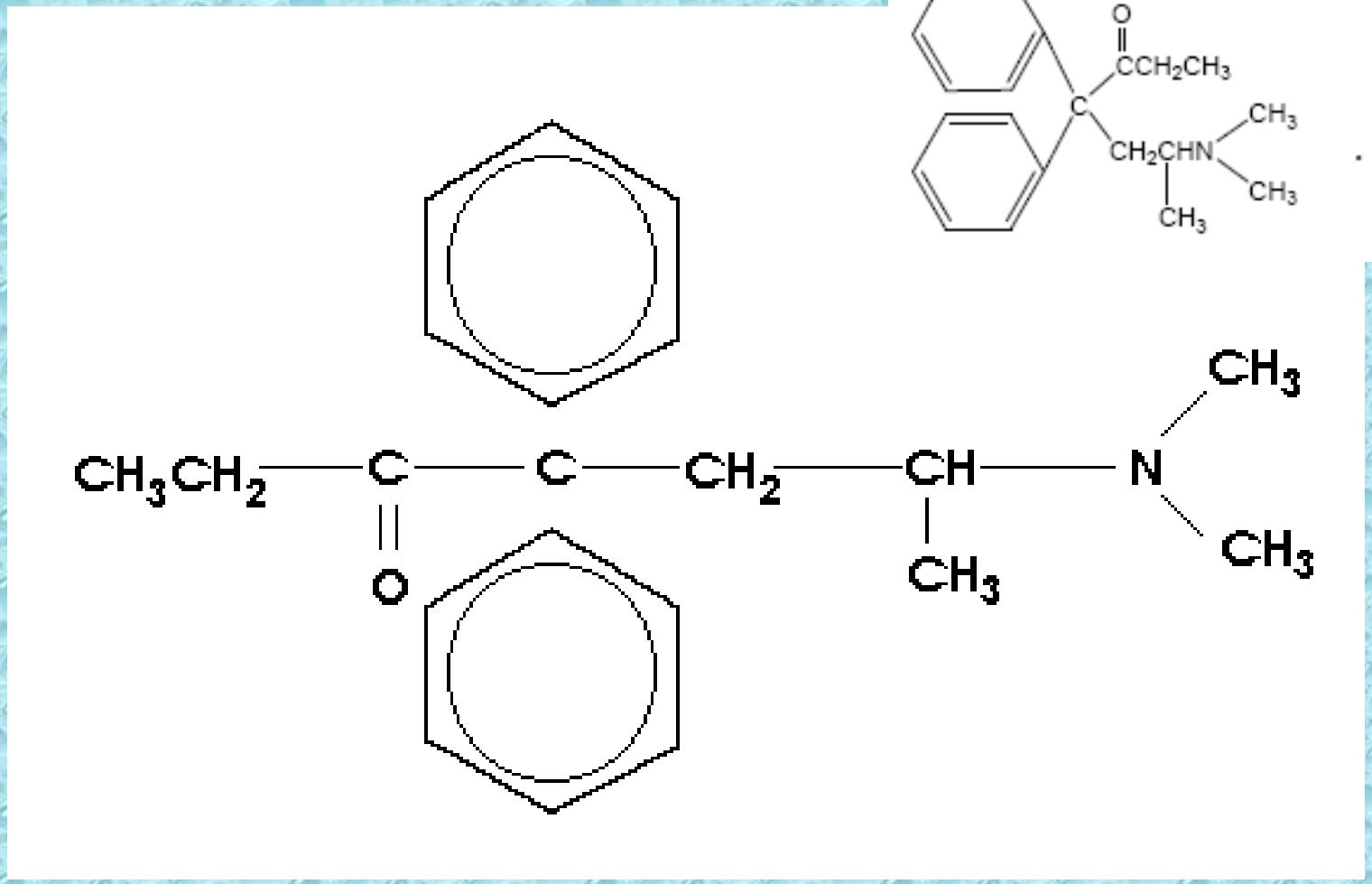
- Most compounds, including opioids exist in two forms of **levo** or **dextro** (i.e., levo-methadone, dextro-methadone).
- One form is **active** and one inactive.
- Active form is usually the levo form and very often levo is dropped from the compounds name.

- All natural and synthetic opioids exhibit a three dimensional T-shaped configuration.
- It has a **methylated nitrogen,**is usually charged at physiological pH.
- The charged nitrogen is essential for activity.
- A hydroxyl group at carbon 3 is also essential. This configuration is called the **piperidine ring**.

the structure of morphine with the piperidine ring indicated by bold lines



Even methadone, which looks strikingly different from other opioid agonists, has steric forces which produce a configuration that closely resembles that of other opiates. **steric forces** bend the molecule of methadone into the correct configuration to **fit into the opiate receptor**.



Pharmacokinetics

- Following oral administration the bioavailability of methadone ranges between 36 to 100% and peak plasma concentrations are achieved between 1 to 7.5 hours and an onset of 30 to 60 minutes.

- It has a relatively high degree of lipid solubility and In plasma, methadone is predominantly bound to α_1-acid glycoprotein (85% to 90%).
- Methadone is secreted in saliva, breast milk, amniotic fluid and umbilical cord plasma.

Half life

- 24 to 36 h in most
- Huge variability so need to treat individual
- Main metabolite EDDP is not active
- Differs from other opioids
  - Heroin 2 mins
  - Morphine 4 hrs

Absorption

- High bioavailability suggests that Absorption of methadone from the Gastro-intestinal tract is almost complete
- Absorption for Oral methadone takes about 0.7h
- High protein and tissue binding however mean that levels of active drug are low between 7-12% of dose

- Methadone is very lipid soluble and thus is readily absorbed when ingested
- Gastric emptying may well be a rate limiting step in the absorption of methadone

Mode of action

- Methadone is a full mu-opioid (mu1 and mu2)agonist and kappa. Methadone also binds to the glutamate NMDA (N-methyl-D-aspartate) receptor, and thus acts as a receptor antagonist against glutamate.

- Glutamate is the primary excitatory neurotransmitter in the CNS.
- NMDA receptors have a very important role in modulating long term excitation and memory formation.

- NMDA antagonists such as ketamine, dextromethorphan, and ibogaine are being studied for their role in decreasing the development of tolerance to opioids and as possible for eliminating addiction/tolerance/withdrawal, possibly by disrupting memory circuitry.

- Acting as an NMDA antagonist may be one mechanism by which methadone decreases craving for opioids and tolerance, and has been proposed as a possible **mechanism** for its distinguished efficacy regarding the treatment of neuropathic pain.

NMDA Antagonists

Very weak

- Paracetamol

Weak

- Some NSAID's
- Methadone
- Pethidine
- Valproate
- Amantidine

NMDA Antagonists

Moderate

- Ketamine
- Dextromethorphan

Strong

- Experimental
- Lethal

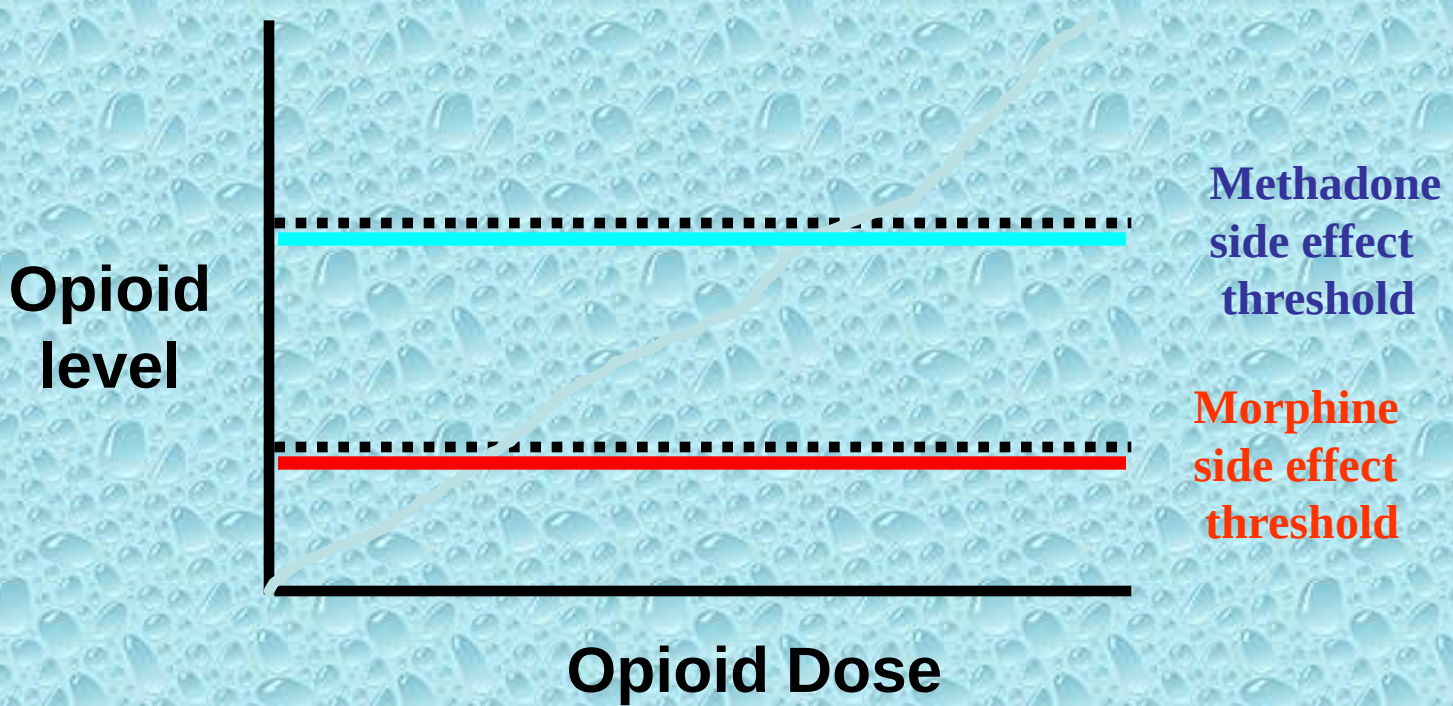
Pain Mechanisms

- opioid receptors
  - μ
    - μ1 analgesia
    - μ2 sedation, respiratory depression
  - δ analgesia, euphoria
  - κ analgesia, sedation

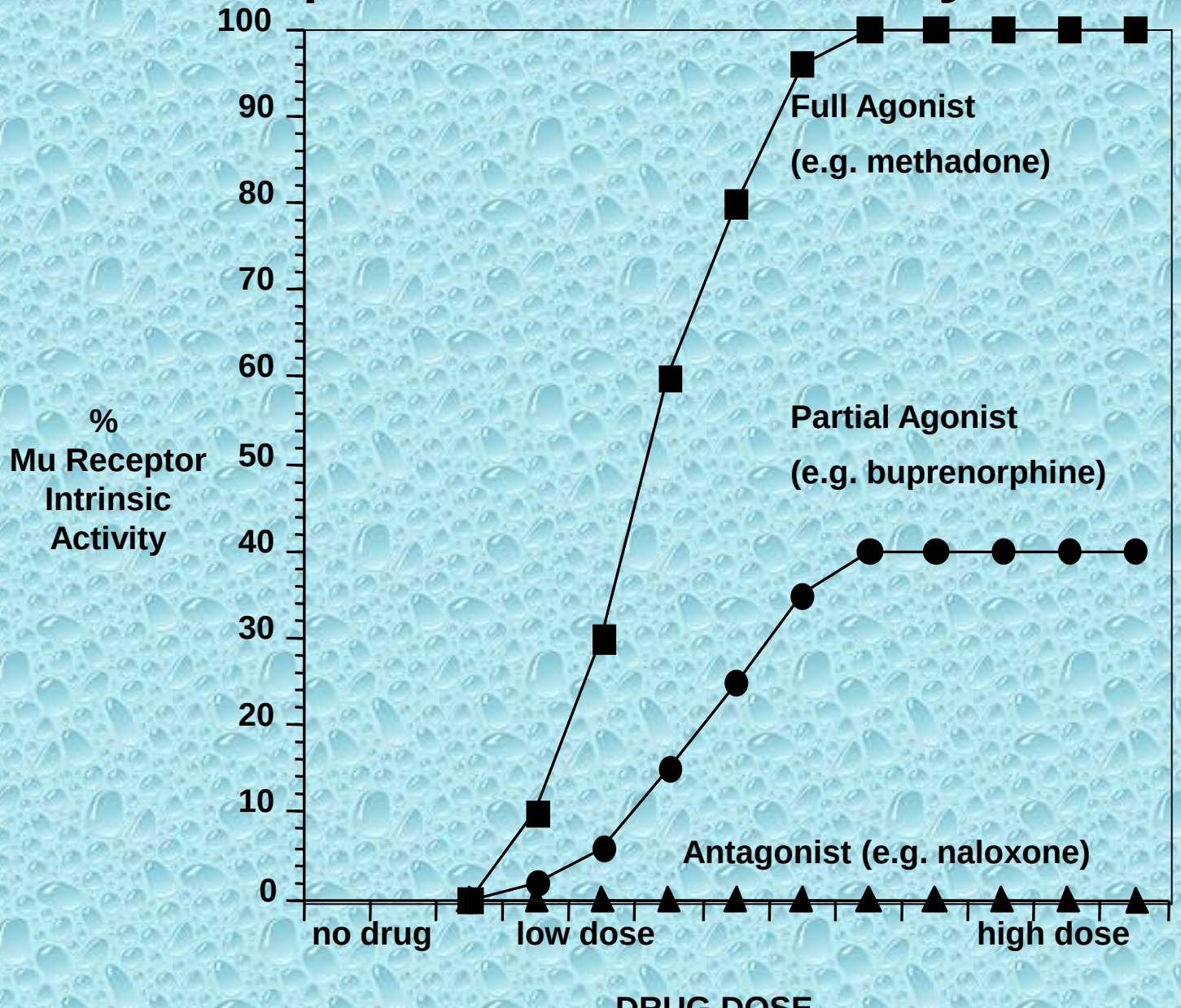
- Methadone may also affect the release of other endogenous neurotransmitters, including acetylcholine, norepinephrine, dopamine, and substance P.
- Methadone provides a level of analgesia and sedation similar to that of morphine, when given in a comparable dose.

- prevents re-uptake of 5-hydroxytryptophan (serotonin) and norepinephrine
- same mechanism by which tricyclics relieve neuropathic pain

Side Effect Threshold



Comparison of Activity Levels



Metabolism

- Methadone has a slow metabolism and very high fat solubility, making it longer lasting than morphine-based drugs.
- Methadone has a typical elimination half-life of 15 to 60 hours with a mean of around 22.

- However, metabolism rates vary greatly between individuals, up to a factor of 100, ranging from as few as 4 hours to as many as 130 hours, or even 190 hours.

- This variability is apparently due to genetic variability in the production of the Cytochrome P450 enzymes CYP3A4 and CYP2B6.CYP2D6, CYP2C9,CYP2C19
- A longer half life frequently allows for administration only once a day in heroin detoxification and maintenance programs.

- Methadone is N-demethylated to EDDP mainly by a liver isoenzyme CYP3A4, Most abundant isoenzyme in the liver
- CYP3A also found in the intestine and contributes to the first pass effect
- CYP3A is not genetically polymorphic – so NO

Fast metabolisers of the drug

Metabolism - First Pass Effect

- Methadone low liver extraction ratio (ER)
- ER = 0.089 due to protein binding
- Only 10-12% of methadone passing through liver is metabolised
- Compare 70% of Morphine (ER = 0.7)

First pass effect

- For most clients, methadone is well absorbed and first pass effect (the amount removed from the body) is minimal (Cl 100-200ml/min)
- Patients with carcinomas had HIGH first pass elimination of methadone (CL>800ml/min)

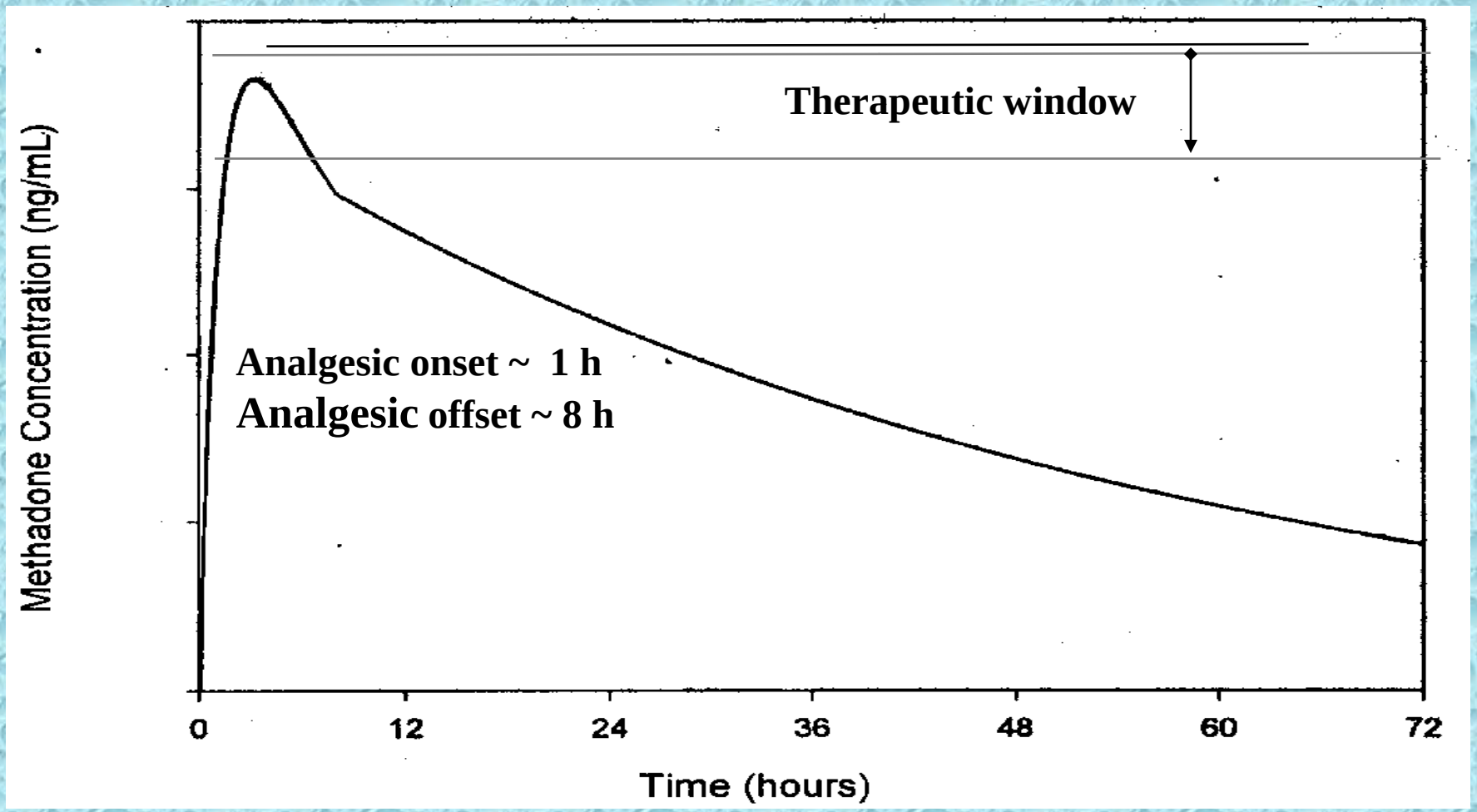
- Patients metabolize methadone rapidly may require twice daily dosing to obtain sufficient symptom.

- The analgesic activity is shorter than the pharmacological half-life; dosing for pain control usually requires multiple doses per day.

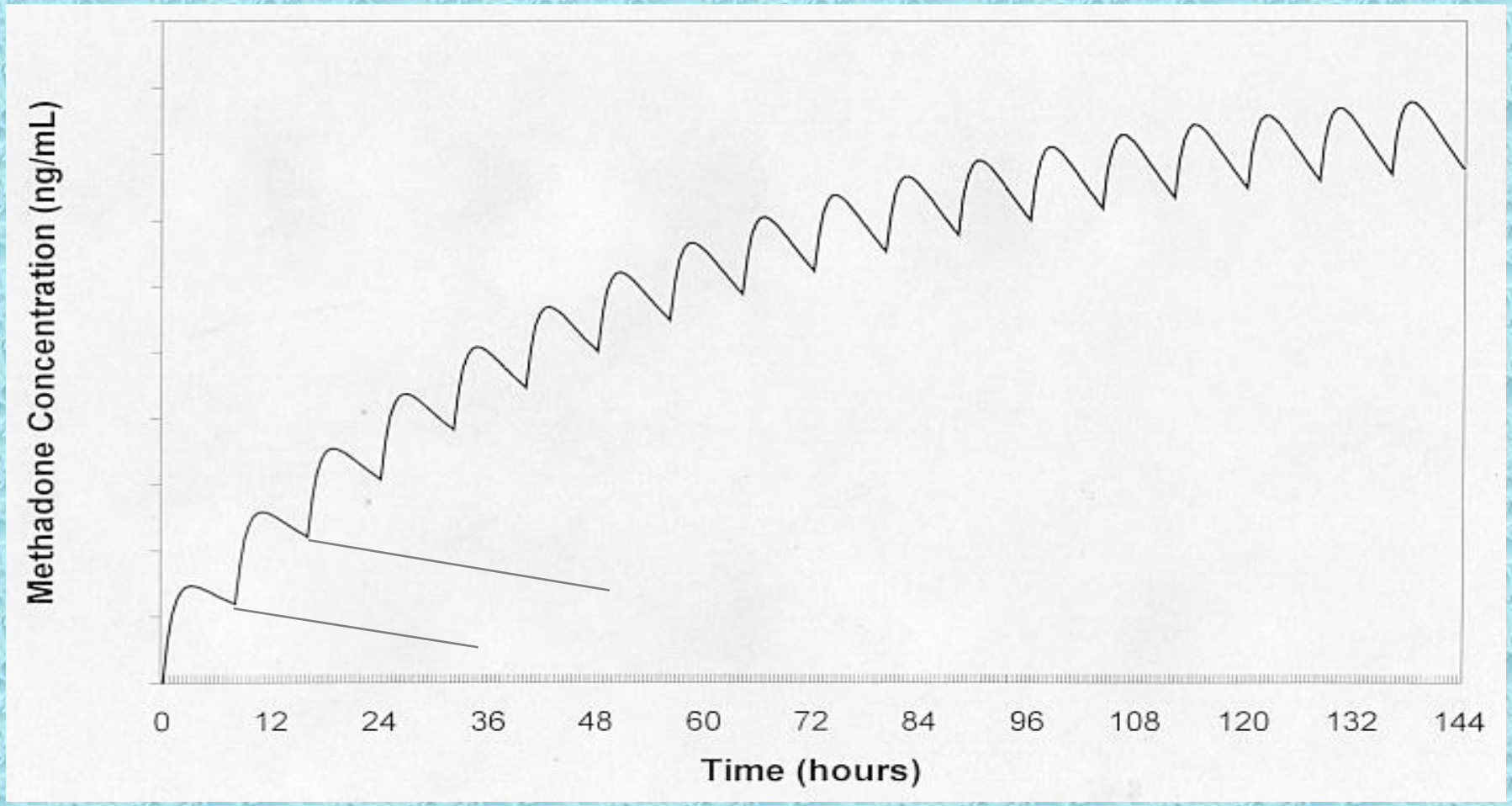
Elimination

- Biphasic elimination
  - alpha (analgesic) $T_{1/2}$ 8-12 hours
  - beta $T_{1/2}$ 24-36 hours - protects against withdrawal
- Risk of accumulation toxicity

Methadone Biphasic Elimination



Plot of Methadone Accumulation
(dosed q 8 h over 6 days)



Adverse effect

- Hypoventilation
- Decreased bowel motility constipation
- miotic pupils
- nausea, sedation, hallucinations, cardiovascular instability, constipation, urinary hesitancy, choreic movements, and hypersensitivity reactions.

- The adverse effects associated with methadone are similar to those of other mu-receptor agonists.
- Respiratory depression can occur with methadone use, and may last for a longer period than that seen with morphine.

Tolerance and dependence

- As with other opioid medications, tolerance and dependence usually develop with repeated doses.
- Tolerance to the different physiological effects of methadone varies.

- Tolerance to analgesia usually occurs during the first few weeks of use; whereas with respiratory depression, sedation, and nausea it is seen within approximately 5-7 days.

- There is no tolerance formed to constipation produced by methadone or other opioids; however, effects may be less severe after time and can often be alleviated through dietary fiber supplements.

withdrawal symptoms

- Withdrawal symptoms of methadone include:
- Increased lacrimation
- rhinorrhea
- sneezing
- nausea
- vomiting
- fever
- chills
- tremor
- tachycardia
- aches and pains, often in the joints

Similar drugs

- Levomethadone, the laevorotary or left-handed stereoisomer of methadone
- It is about eight times stronger than the racemic drug and is marketed especially in continental Europe as an analgesic under the trade names **Levo-Polamidone, Polamidone, Heptanone, Heptadone, Heptadon** and others.

- The synthetic compound levo-α-acetylmethadol (or LAAM) has an even longer duration of action (from 48 to 72 hours), permitting a reduction in frequency of use.
- In 1994 it was approved as a treatment of narcotic addiction.

LAAM:
Levo-Alpha Acetylmethadol
A Long-Acting Opiate Agonist

- **Pharmacological Action**
  - ✓Metabolites more active than parent drug
- **Advantages**
  - ✓One dose lasts 48 to 72 hours
  - ✓Fewer trips to the clinic
  - ✓Better heroin blockage
- **Disadvantage**
  - ✓Cardiac complications

- Other analogues of methadone which are still in clinical use are dipipanone (Diconal) and dextromoramide (Palfium) which are shorter lasting than methadone but considerably more effective as analgesics.

- These drugs have a high potential for abuse and dependence and were notorious for being widely abused.
- They are still rarely used for the relief of severe pain in the treatment of terminal cancer or other serious medical conditions.

Pharmacokinetics in Special Populations

- ***Pregnancy***
- The disposition of oral methadone has been studied in approximately 30 pregnant patients in 2nd and 3rd trimesters.
- Elimination of methadone was significantly changed in pregnancy. Total body clearance of methadone was increased in pregnant patients compared to the same patients postpartum or to non-pregnant opioid-dependent women.

- The terminal half-life of methadone is decreased during 2nd and 3rd trimesters.
- The decrease in plasma half-life and increased clearance of methadone resulting in lower methadone trough levels during pregnancy can lead to withdrawal symptoms in some pregnant patients.
- The dosage may need to be increased or the dosing interval decreased in pregnant patients receiving methadone.

Renal Impairment

- Methadone pharmacokinetics have not been extensively evaluated in patients with renal insufficiency.
- Unmetabolized methadone and its metabolites are excreted in urine to a variable degree.
- Methadone is a basic (pKa=9.2) compound and the pH of the urinary tract can alter its disposition in plasma.

- Urine acidification has been shown to increase renal elimination of methadone.
- Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for increasing the elimination of methadone or its metabolites.

Hepatic Impairment

- Methadone has not been extensively evaluated in patients with hepatic insufficiency.
- Methadone is metabolized by hepatic pathways, therefore patients with liver impairment may be at risk of accumulating methadone after multiple dosing.

- ***Gender***
- ***Race***
- The pharmacokinetics of methadone have not been evaluated for gender and race specificity.
- ***Geriatric***
- ***Pediatric***
- The pharmacokinetics of methadone have not been evaluated in the geriatric and pediatric population.

Drug Interaction

- Methadone undergoes hepatic N-demethylation by cytochrome P-450 isoforms, principally CYP3A4, CYP2B6, CYP2C19, and to a lesser extent by CYP2C9 and CYP2D6.

- Coadministration of methadone with inducers of these enzymes may result in more rapid methadone metabolism, and potentially, decreased effects of methadone.
- Conversely, administration with CYP inhibitors may reduce metabolism and potentiate methadone's effects.

- Pharmacokinetics of methadone may be unpredictable when coadministered with drugs that are known to both induce and inhibit CYP enzymes. Although antiretroviral drugs such as efavirenz, nelfinavir, nevirapine, ritonavir, lopinavir+ritonavir combination are known to inhibit some CYPs, they are shown to reduce the plasma levels of methadone, possibly due to their CYP induction activity.

- Therefore, drugs administered concomitantly with methadone should be evaluated for interaction potential; clinicians are advised to evaluate individual response to drug therapy before making a dosage adjustment.

- due to inducers or inhibitors of CYP450
  - TB drugs: lower methadone level
  - Antiretrovirals: lower level
  - antifungals (Diflucan™): raise level
  - phenytoin, Tegretol™: lower level
  - SSRIs: raise level
  - resperidone: lowers level

Methadone maintenance treatment

- The principal effects of methadone maintenance are to relieve narcotic craving, suppress the abstinence syndrome, and block the euphoric effects associated with heroin.
- Methadone maintenance has been found to be medically safe and nonsedating.
- It is also indicated for pregnant women addicted to heroin.

Effects

- At proper dosing, methadone usually reduces the appetite for and need to take heroin.
- Furthermore, higher doses, generally above 120mg, provide cross-tolerance and block the euphoric effects of other opioids such as heroin, greatly reducing the motivation of patients to use them.

- A proper dose used in methadone maintenance therapy will block or greatly reduce cravings and illicit opioid use while not inducing any euphoric feelings or other subjective sense of being high, and if high enough will actively prevent the patient from experiencing any high if they do use other opioids.

Difficulties in Methadone Use

- high interindividual variability
  - equianalgesic doses vary widely person-to-person and day-to-day/week-to-week in same person
- long half-life
- varying level of plasma binding protein
- age, gender, weight (large distribution reservoir)
- other medications
- time from start of treatment (auto-induction)

Reasons to Use Methadone

- effective in intractable pain
- low level of toxic side effects
- available as long-acting liquid
  - can dose BID in patients with dysphagia
- low cost

Reasons to Use Methadone

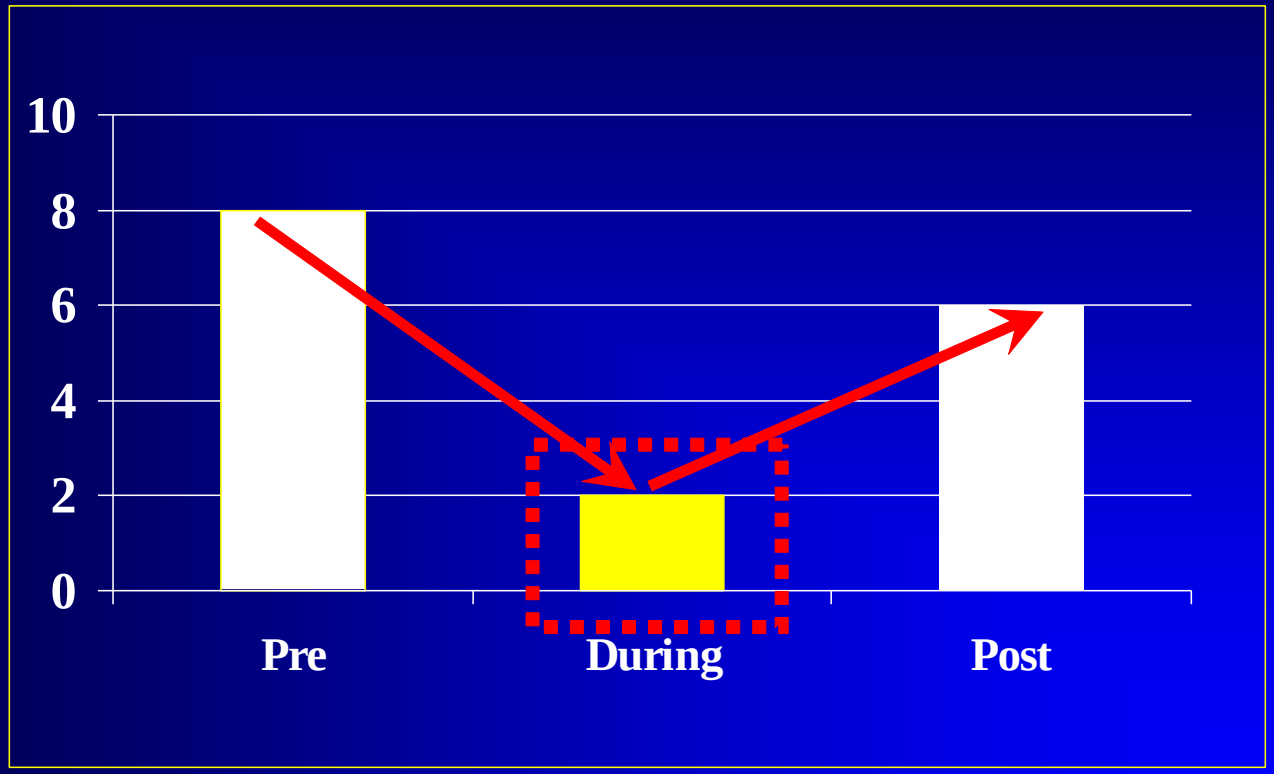
MS Contin™	1000mg/d	$820
Kadian™	1000mg/d	$960
OxyContin™	800mg/d	$1066
Duragesic™	250mcg/h	$1499
Methadone tabs	100mg/d	$22

Heroin vs Methadone

-

	Heroin	Methadone
Route of administration	intravenous	oral
Onset of action	immediate	30 minutes
Duration of action	3–6 hrs	24–36 hrs
Euphoria	first 1–2 hrs	none
Withdrawal symptoms	after 3–4 hrs	after 24 hrs

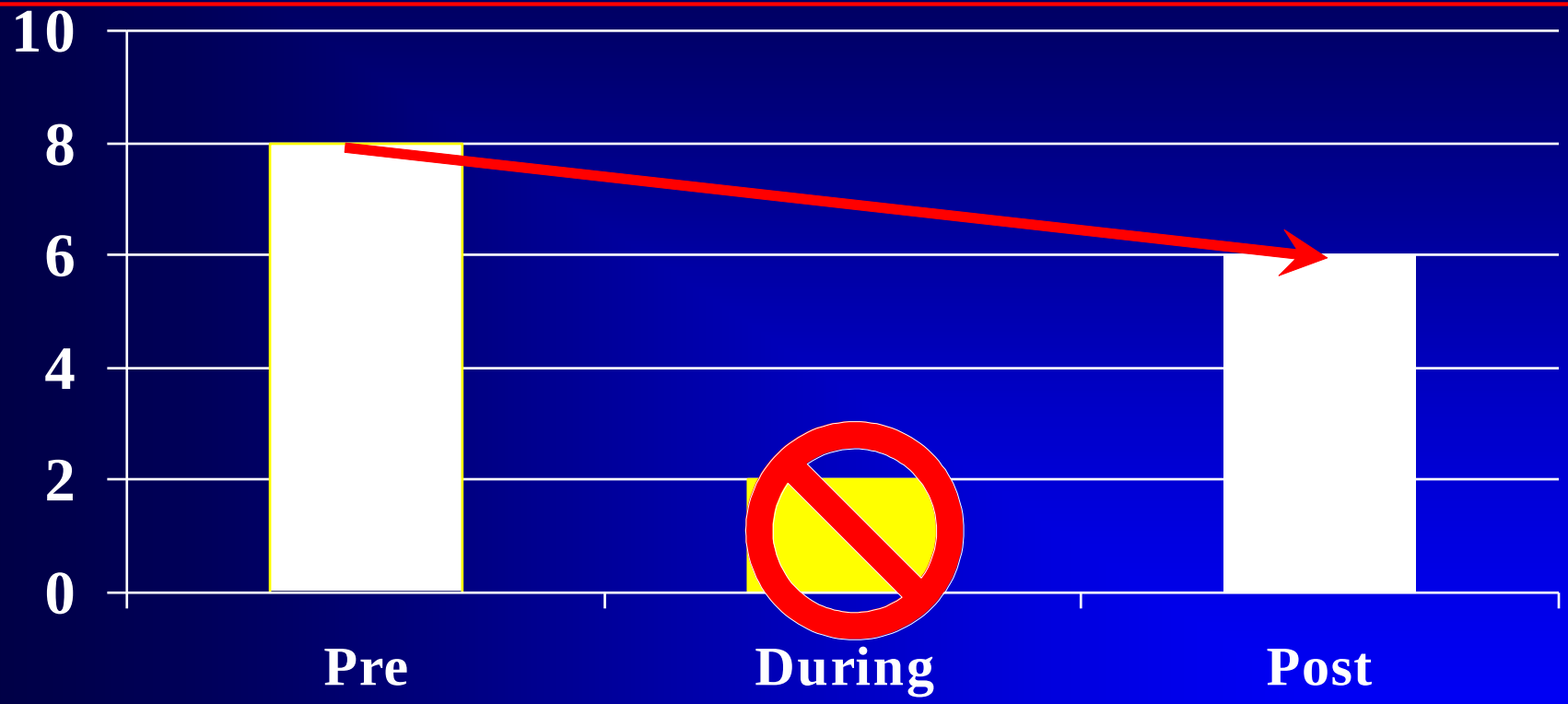
Outcome In Diabetes



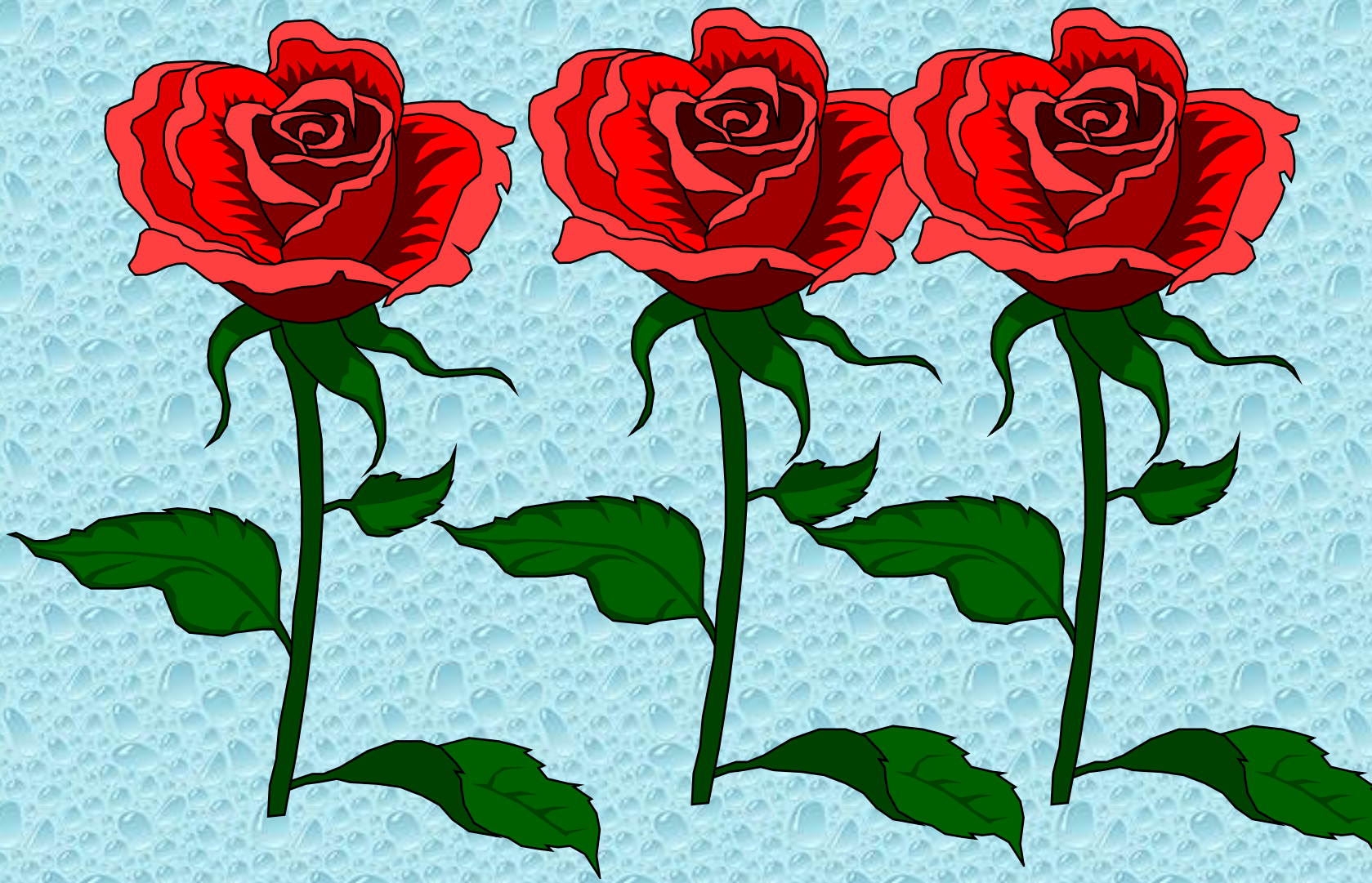
Conclusion: Treatment Successful!

Treatment Research Institute

Outcome In Addiction



(Incorrect) conclusion: Treatment NOT successful!



THANK YOU!

What are the symptoms of methadone overdose?

- muscle spasticity
  difficulty breathing
  slow, shallow and labored breathing
  stopped breathing (fatal within 2-4 hours)
  pinpoint pupils
  bluish skin and fingernails and lips
  spasms of the stomach and intestinal tract
  constipation
  weak pulse
  low blood pressure
  drowsiness and disorientation

Dosing Models

- Edmonton PC Unit
  - decrease current opioid by 1/3 each day
  - use 10:1 MS:methadone equivalent
  - as MS decreases, increase methadone dose give q 8 hrs
  - BT pain: 10% of methadone daily dose
  - increase methadone dose q 3 days only if pain is >7-8

Dosing Models

- UK Hospice Model
  - stop current opioid
  - start methadone on fixed dose q 3 hrs prn
    - 1:10 ration (per dose) if <300 mg MS
    - 30 mg methadone is highest initial fixed dose
  - on day 6 calculate total methadone given over past 48 hours and convert to BID schedule

Dosing Models

- H&PC of Metropolitan Washington Model
  - stop current opioid
  - start methadone 1:10 ration
    - 1:20 if pt elderly or MS >1000 mg
  - 50 mg is highest starting dose, q 3 hrs prn
  - change to q 8 dosing when pain controlled

Dosing Models

- Milan Model (Ripamonti/Mercadente)
  - similar to Edmonton except different ratios
  - <100 mg MS = 4:1 methadone
  - 100-300 mg = 8:1
  - 301-600 mg = 12:1
  - 601-799 mg = 15:1
  - >800 mg = 20:1

Dosing Models

-Calculate total daily dose of methadone

-Stop current opioid

-Start methadone, dividing total dose into 3 q 8 hr doses

-Breakthrough dose is 10% of total daily dose given q 3-4 hrs prn

-Adjust dose only q 5 – 7 days

Using Methadone

- multiple models because drug has wide variability
- “start low, go slow” good rule-of-thumb
- find model that works for you
- watch for respiratory depression
- do not fear drug; use good medical/nursing practice

Treatment Philosophy

- In Britain to prescribe a dose that will prevent withdrawal symptoms for the whole dosing interval = low dose
- In USA to prescribe a dose that will block euphoric effects of heroin = high dose

Injectable methadone

- Higher plasma concentrations to dose observed
- Due to shunt metabolism at gut level and of liver first pass effect.
- Due to diminished influence of interindividual variability in metabolism

(Felder et al, 1999)

Methadone & Alcohol

- Alcohol use:
  - Bingeing (acute high intake) will induce methadone withdrawal symptoms
  - Educate client
  - Alcohol dependence – may need higher dose if liver enzymes affected
  - Not a good mix – poor prognosis

Treatment - Dosage Assessment

- Metabolism of methadone at the onset of treatment is significantly slower than after dosing has reached steady-state conditions (9-14 days).
- Risk of accumulation during first few days of treatment (Wolff et al, 2000)
- Deaths reported in Australia

Drug – Drug Interactions

- Drugs which induce CYP3A4 speed up metabolism of methadone
- Clinically important interactions
  - Rifampicin
  - Phenytoin
  - Carbamazepine
  - Phenobarbitone

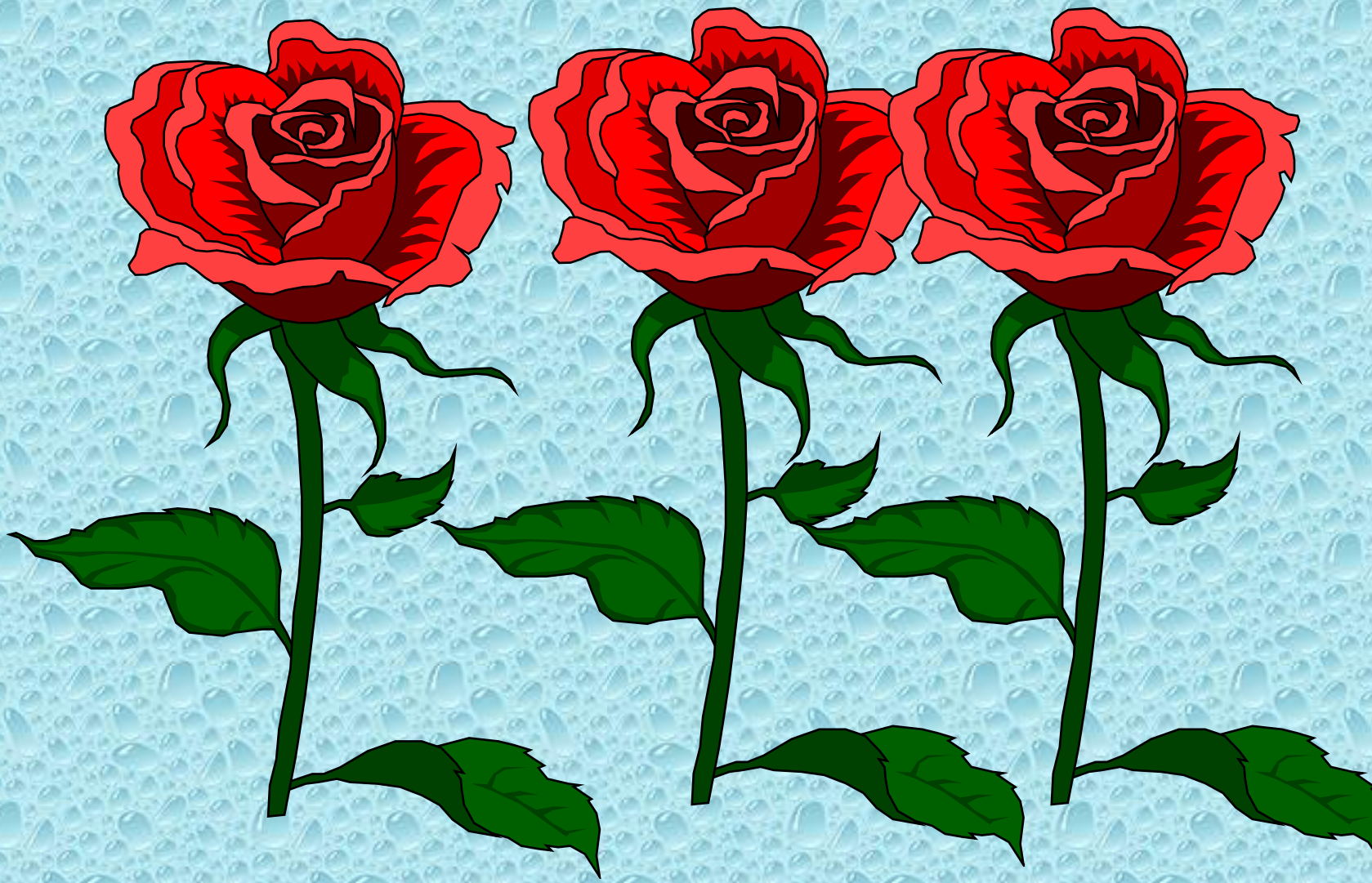
Drug inhibitors

- Protease inhibitors e.g., Ritonavir, Zidovudine.
  - Antidepressant – desipramine (raised plasma levels of desipramine)
  - Antibiotics - erthromyocin
  - Histamine H_2-antagonists (Cimetidine and Rantitidine).
  - Selective serotonin re-uptake inhibitors (SSRIs e.g., Sertraline, Fluvoxamine)
  - Anti-infective agents eg Fluconazole

- **Monoamine Oxidase (MAO) Inhibitors** - Therapeutic doses of meperidine have precipitated severe reactions in patients concurrently receiving monoamine oxidase inhibitors or those who have received such agents within 14 days. Similar reactions thus far have not been reported with methadone. However, if the use of methadone is necessary in such patients, a sensitivity test should be performed in which repeated small, incremental doses of methadone are administered over the course of several hours while the patient's condition and vital signs are under careful observation.
- **Desipramine** - Blood levels of desipramine have increased with concurrent methadone administration.

Tolerance

- Risk of overdose increases if doses are missed due to reduction in tolerance
- Increased risk if use with Alcohol and Benzodiazepines (Dizaepam)
- Risk increased after Custodial sentence or at the start of treatment,



THANK YOU!